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HEPATITIS A IMMUNITY IN U.S. TRAVELERS: PREVALENCE AND ASSOCIATED FACTORS

Alain-Marc Werner

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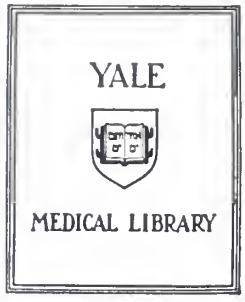
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HEPATITIS A IMMUNITY IN U.S. TRAVELERS: PREVALENCE AND ASSOCIATED FACTORS

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Alain - Marc Werner

1991

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Abstract

Hepatitis A remains a significant problem in travelers to developing nations. Immune serum immunoglobulin (ISIG), administered intramuscularly, is an effective form of prophylaxis but must be given every 5-6 months for extended stay or repeat travelers. Although the prevalence of immunity to hepatitis A in developed nations is relatively low, certain subgroups of the travel population may have a high enough prevalence of immunity to render screening a reasonable alternative to routine ISIG prophylaxis. Previous studies of British travelers have indicated that older patients, those of Asian descent, and those with a history of jaundice, may fulfill such criteria. Such criteria in U.S. travelers have not been studied.

A retrospective study of patients at two U.S. university-affiliated travel clinics was performed to assess the value of certain indicators in past medical and travel history to predict immunity to hepatitis A. 762 patients above the age of 16 seen in either clinic were tested for hepatitis A antibody during 1987-1990. 112 immune subjects (15%) were identified. 61 immune individuals aged 18 to 81 and 121 non-immune individuals, aged 17-71, were studied. Of the 61 immune subjects, 48(79%) were over the age of 40, whereas 50(41%) of the non-immune subjects were over the age of 40 ($p<.0005$) (odds ratio 5.2, 2.7-10.2, 95% CI). Twenty-two (36%) of the immune individuals were born outside of the U.S., whereas 14 (12%) of the non-immune individuals were born outside of the U.S. ($p<.0005$)(odds ratio 4.3, 2.1-8.9, 95% CI). Nineteen (31%) of the immune individuals gave a history of hepatitis whereas two (2%) of the non-immune individuals gave such a history ($p<.0005$)(odds ratio 26.2, 9.0-80.3, 95% CI). Fifty-three (87%) of immune individuals gave a history of previous travel to developing nations whereas 75 (62%) of non-immune individuals gave such a history ($p<.001$)(odds ratio 4.1, 1.9-9.0, 95% CI). Screening for immunity may be an appropriate alternative to routine ISIG prophylaxis in extended stay or repeat U.S. travelers if they are >40 years old, were born outside of the U.S., or give a history of hepatitis or of travel to developing nations.

Introduction

Hepatitis A is a significant complication of travel to the developing nations. A lower prevalence of immunity in the developed nations, combined with a higher incidence of disease and poorer sanitation measures in the developing nations renders unprotected travelers susceptible to contracting hepatitis A. Current Centers for Disease Control (CDC) recommendations call for passive immunization with pooled serum immunoglobulins(ISIG), which is an effective means of prophylaxis for these travelers. However, ISIG prophylaxis must be repeated every four to six months and is unnecessary and inconvenient for patients who have already developed a natural, active and lifelong immunity. Several studies performed in England have suggested that certain subpopulations of travelers to developing nations have a high enough prior probability of immunity to render serological testing a cost-effective screen. The purpose of this study was to search for factors in the past medical and travel history of patients at American travel clinics which might be associated with immunity. Determination of such factors might allow the clinician to use the patient interview to identify patients with a greater chance of immunity than that of the general population. Although this study is not designed to quantitatively assess the cost-effectiveness of serological testing in these patients, it provides the clinician with qualitative information that may enable him or her to spare the patient unnecessary ISIG injections.

In this introduction, the clinical importance of hepatitis A will first be reviewed, followed by a description of the risks posed to the U.S. travel clinic patient of contracting the disease. These risks are not well-quantified, and few studies even attempt to measure their magnitude. The effectiveness and safety of ISIG prophylaxis will then be addressed, as well as the importance of other considerations regarding its use. Finally, studies in England considering the prevalence of hepatitis A immunity in travel clinics and the costs of screening and prophylaxis will be reviewed, for their significance in the design of this study.

Clinical Importance of Hepatitis A

Epidemiology in General Population

Hepatitis A is one of the less morbid hepatitides but is still of considerable clinical significance. 21,532 cases were reported to the CDC in 1983 and of the 7854 serologically confirmed cases, 33.2% were hospitalized and 0.6% died. In comparison, 1.6% of 8925 serologically confirmed cases of hepatitis B (24318 cases in total) ended in death and 44.4% were hospitalized. 6.1% of the cases of hepatitis A reported in that year were attributed to international travel (1).

Etiology

The disease is caused by a 27 nanometer nonenveloped RNA picornavirus which is quite resistant to inactivation by physical and chemical means (2). Although the natural means of transmission of the virus is considered to be fecal-oral, parenteral inoculation is a successful method of inducing infection in experimental animals and in test subjects. Within one to two weeks after inoculation by either route, virus

is present in the liver, serum and stool (3). Fecal excretion and viremia generally disappear within days of the arrival of symptoms, at about four weeks after inoculation (4,5). Jaundice and elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) appear at about this time, as well as anti-hepatitis A virus (HAV) IgM, as determined by enzyme-linked immunosorbent assay (ELISA)(6). The jaundice, elevated transaminases and symptoms are usually completely resolved by approximately three months after inoculation, whereas anti-HAV IgM persists in up to 30% of subjects (93% in one study) at six months after inoculation(7,8,9). Anti-HAV IgG appears at about four weeks after inoculation and probably persists for life, conferring active immunity on the subject(10).

Clinical Presentation

The spectrum of presentation is quite varied. Fulminant hepatitis A is rare and is associated with jaundice, dark urine, abdominal pain and nausea(11). As the prevalence of immunity in adult populations is much higher than the number of positive histories of jaundice or hepatitis would suggest, a large number of cases of hepatitis A must be asymptomatic. Hadler(12) found a rate of 84%, 50% and 20% of asymptomatic infections for day-care children aged 2, 3 to 4 and over 5 years, respectively, while 11% of inoculated adult volunteers were found to be asymptomatic(13). A recent Chinese study of preschool children subjected to a common-source exposure to hepatitis A found that 25% of the children had an inapparent infection documented only by the presence of anti-HAV IgM or a change in anti-HAV IgG titers, while 50% of the children demonstrated a change in ALT and another 25% of the

children had clinical symptoms and jaundice. All children were found to be excreting HAV in their stools(14). Thus, both extremes of expression of hepatitis A are clinically significant for travelers. Hepatitis A can cause death, as well as cause a large number of asymptomatic infections. Furthermore, it is clear that a significant proportion of infected individuals may produce infectious stools without any overt signs of disease.

Attempts to Assess and Control Risk to Unprophylaxed U.S. Travelers of Contracting Hepatitis A During Travel to Developing Nations

The risk of travelers from the developed countries contracting hepatitis A during travel to the developing nations depends on several factors, most of which have been poorly quantified. First, the prevalence of immunity among the travelers themselves must be considered, along with the incidence of infection in a given region of travel. The epidemiological pattern of infection in a given region, and putative explanations for this pattern may be even more important than reported incidences. The behavior of the travelers will determine the extent to which they expose themselves to the risks of infection posed by the environment and individuals in the region of travel. Finally, the efficiency of immunoprophylaxis, if given, must be considered.

Prevalence of Immunity/Susceptibility in the U.S.

In the United States, a wide range of prevalences of anti-HAV IgG has been reported(15,16). Prevalence increases with increasing age and with decreasing socioeconomic status. Thus, for example, less than 10% of middle-class children tested in 1976 were HAV immune as compared to

nearly 75% of middle-class adults over 50 years old. Among poor, black populations in New York City, prevalence rose from 50% to over 75% in subjects aged 20 to over 50 years. Other factors have been suggested as playing a role as well. Foreign-born individuals had an age-adjusted prevalence of 75% in these studies, as compared with 31% in American-born individuals. Middle-class whites with serological evidence of exposure to hepatitis B had a higher prevalence (54%) than those without such evidence (31%). In these studies, homosexuals did not have a higher prevalence. Furthermore, only 3-5% of HAV immune subjects gave a history of hepatitis(15,16).

These data suggest that, to the extent that a travel clinic population represents a cross-section of American society, a significant fraction of a travel clinic population would not be immune to hepatitis A, and would therefore be susceptible to contracting the disease during travel to developing nations. On the other hand, socioeconomic profiles of U.S. travel clinic populations in general, or the populations in this study are not available to confirm or refute the assumption that they represent a cross-section of U.S. society. However, since international travel is costly and since attendance at travel clinics usually requires self-payment by the patient, the socioeconomic status of our travel clinic population is probably higher than that of the general U.S. population. This would suggest that even a greater proportion of these travelers would be non-immune.

In any case, these data demonstrate that there is no group in which the immune status of an individual could be a virtual certainty based on membership in that group. Furthermore, these studies were completed

in the mid-1970's and prevalence among the younger age-groups might be substantially lower now. Indeed, the incidence of symptomatic hepatitis A is currently one case per 100,000 person-years, which would suggest that the prevalence of immunity among younger age-groups is now very low(17). Thus, in the absence of serological testing, the CDC recommends routine ISIG prophylaxis for all travelers to developing nations. How these prevalence data might render the serological testing of certain subgroups a reasonable alternative to ISIG prophylaxis, however, will be discussed later.

Incidence and Prevalence of Hepatitis A in Developing Nations

The true incidence of infection in the developing nations is also important in determining the risks for travelers of contracting hepatitis A. The lack of a carrier state and the short period of fecal shedding renders only currently infected individuals contagious either through personal contact or through contamination of food or water supplies. However, data on incidence is more difficult to collect than is data on prevalence. Furthermore, because hepatitis A is often an asymptomatic disease, reported incidence may give a misleading indication of how many people might actually be shedding virus at any one time. For example, a study in Israel demonstrated an increase in incidence of viral hepatitis from 0.8 to 1.2 cases per 1000 in the years 1951-1985 during which sanitary conditions had improved(18). An increase in the rate of reporting might explain these findings or, as the authors suggest, improved sanitary conditions may have caused the age of peak incidence to increase from the 1-4 year old age group to the 5-9 year old age group,

when more infections are symptomatic. Thus, the number of people shedding virus might have decreased despite the apparent increase in incidence. A similar pattern was hypothesized for poliomyelitis following the sanitary improvements of the 20th century. On the other hand, an improvement in sanitary conditions of San Roma, Costa Rica was used to explain the drop in incidence of viral hepatitis in that city, from 253 to 25 annual cases between the years 1973-1980(19). In neither of these two studies is serological type reported, which further emphasizes the difficulty in interpreting data such as these.

Seroprevalence in very young populations could also be used as an indicator of the current, true incidence. A study of schoolchildren in Naples, Italy showed a decline in prevalence of anti-HAV IgG from 20.0% to 5.2% of seven-year olds between the years 1980 and 1988. These data came from different, albeit socioeconomically similar, districts and the change was attributed to improvement in sanitation(20). In contrast, in several small villages in the Andes, a prevalence of 86.9% was seen even in the 1-5 year-old age group, with no statistically significant differences between age groups, leading one to believe that hepatitis A continues to be hyperendemic in this region(21).

Patterns of Infection in Developing Nations

It is clear that quantitative assessments of infection rates in developing countries are rare and difficult to interpret. Thus, immunoprophylaxis is recommended for travel to all developing nations, and the classification of nations as "developing" is left ot the judgment of the clinician. Some greater discretion might be attained by classifying regions where

hepatitis A is present in hyperendemic, endemic and epidemic form. For example, in the villages in the Andes, with a uniformly high prevalence rate in young children, hepatitis A is hyperendemic, signifying that exposure is universal by a very young age, presumably because sanitation is poor enough to allow continual common-vehicle transmission. Because of the young age at transmission, virtually all infections are asymptomatic. Apparently, although these populations would be expected to be small and isolated, the number of susceptibles is never exhausted. Otherwise, periodic re-introduction of the virus, with resulting epidemics and significant numbers of symptomatic cases would have to be postulated for such a high prevalence. In hyperendemic regions, a traveler would have a high risk of being exposed to HAV in drinking water, food and even personal contact.

Endemic regions are those in which sanitation has improved enough so that common-vehicle transmission becomes less important than person-to-person transmission. Most cases are asymptomatic, which facilitates spread, but first exposure may occur at later ages, and so some cases will be symptomatic, giving rise to the appearance of small epidemics. Indeed, regions in which hepatitis A is solely epidemic are those in which there is a large susceptible population because of a low recent incidence, which could be caused by minimal opportunities for common-vehicle or person-to-person transmission. Epidemiologic data from the developed countries suggests that hepatitis A is primarily an epidemic disease, and that continual, serial transmission or common-vehicle transmission is prevented by public health surveillance. Because of the difficulty of determining the incidence of asymptomatic infection, it is

difficult to classify regions where hepatitis A is endemic, however, many nations which are steadily improving their sanitation systems are probably passing through a phase of endemicity(47). Israel may be an example of such a nation. Travelers to endemic regions are at risk of exposure to HAV from personal contact with recently infected, albeit asymptomatic individuals. However, as in epidemic regions, the traveler is also at risk from large common-source outbreaks as occurs, for example, when water supplies are contaminated during accidental release of sewage during floods.

Again, although the clinician may try to classify regions as hyperendemic, endemic and epidemic and apprise the patient of the risks in each region, quantitative data that would allow for an accurate determination of risk are not available. One might otherwise attempt to quantify a traveler's risk of contracting hepatitis A in terms of his or her exposure to the vehicles of transmission. It is generally accepted that hepatitis A is spread by the fecal-oral route and therefore, that infectious fecal contamination of food or water or parts of the body that, unwashed, will have contact with the mouth, is the means of spread.

Vehicles of Transmission

Contamination of the water-supply is a well-recognized cause of epidemics, although waterborne outbreaks account for less than 1% of the total number of reported cases of hepatitis A(24). Although the WHO has recommended treating drinking water with a free chlorine residual of 0.3-0.5 mg/Liter for 30 minutes and isolating no viruses per 100 to 1000 liters of drinking water, water with a free chlorine residual of 0.2-

0.8 mg/L that was then contaminated in the distribution system and associated with a huge hepatitis A outbreak in India was found to have other viruses in concentrations of 1-7 plaque-forming units per 12-40 L of drinking water(24,25). Thus, even in regions where water is treated, the traveler is at risk when sewage contamination of the water system occurs, as sometimes occurs during monsoon flooding. Travelers are also at risk where water is not treated or chlorinated. Aside from the risks of obvious contamination with human waste, ponds and wells in Ghana and China have been shown to contain Enterovirus even though there was no known source. Contaminated water is also known to spread hepatitis A when used to clean dishes or when used in aerosol irrigation. Finally, recreational activites associated with contaminated lakewater have been implicated in one outbreak of hepatitis A(26).

The traveler can reduce risk by not drinking or using potentially contaminated water. Portable chemical additives such as sodium hypochlorite (10mg/L), iodine (3mg/L) and potassium permanganate (30mg/L) have been found to inactivate hepatitis A in contaminated drinking water. Boiling water will also kill the virus(2).

Another source of hepatitis A infection is foodborne virus. This is generally associated with shellfish, which are often eaten uncooked and which, in fecally contaminated water, can concentrate the virus to an infectious level. Information about the risk in developing nations is lacking; in the U.S., however, shellfish outbreaks accounted for less than 4% of cases in 1981(27). As the virus can withstand temperatures of 60' C for 60 minutes, even steaming shellfish is unlikely to

decontaminate it. Other food products, primarily uncooked, have been associated, if rarely, with hepatitis A outbreaks(26).

Contaminated food-handlers are another possible source of infection. Contaminated foodhandlers accounted for 7% of cases in the U.S. in 1981(27). Several states in the U.S. require restauraunt employees to wash their hands before returning to work after using toilet facilities, but it is difficult to quantitate the effect such behavior or lack thereof would have on the international traveler. A recent study found no increased incidence of hepatitis A in " adventure " travelers who lived in cheap accomodations or camped, as opposed to travelers who stayed in international level hotels, which may suggest a limited role for foodhandler transmission as well as for use of untreated water(28).

Ordinary person-to-person contact is an unlikely mode of spread unless one person is fecally incontinent or his or her hands otherwise become fecally contaminated. The only healthy people who are consistently fecally incontinent are young children and thus, person-to-person contact is a frequent mode of spread in the context of day-care center outbreaks. Since some long-term travelers place their children in day-care centers, these travelers are at risk of contracting hepatitis A from their young, untoilet-trained children. The risk is especially pronounced since children, as well as adults in endemic regions are very likely to have asymptomatic infections. Homosexual sexual relations are considered to be a form of person-to-person contact that abets the transmission of hepatitis A. No such predilection has been demonstrated among travelers, however. Likewise, parenteral modes of transmission have only rarely been documented for hepatitis A and have not been reported in

travelers. Thus, no recommendations about personal contact with natives that would substantially alter risk can be made.

It is clear from this discussion that quantifying a traveler's risk of contracting hepatitis A based on exposure to the vehicles of transmission is difficult. A clinician can warn a patient to avoid consuming water or food that might be fecally contaminated, or to be wary of certain types of personal contact, but specific quantitative data that would allow the clinician to reject ISIG prophylaxis on the basis of expected forms of exposure during travel do not exist.

Incidence of Hepatitis A in Travelers from Developed Nations During Travel to Developing Nations

Although the importance of individual risks is difficult to quantitate, there have been several studies that have been able to provide some information on the incidence of hepatitis A in travelers from the developed nations. A preliminary study of American travelers in 1972 revealed an incidence of 15 cases in 26119 (57 per 100,000) overseas travelers abroad for one month. This rate of approximately 70 per 100,000 person-years is seventy times greater than the incidence calculated for the U.S. population in the decade 1971-1980(17). No correlation between infection and any aspect of type, location or duration of travel was provided, however(29).

A Swedish study demonstrated a hepatitis A attack rate in 1980 of 1.4 per 1000 and 10 per 1000 unprophylaxed travelers to Northern Africa and Tropical Asia or Africa, respectively(30). The attack rate for unprophylaxed travelers to southern Europe in 1980 was 0.17 per 1000,

down from 0.33 per 1000 in 1965-1974, a trend attributed by the authors to improved socioeconomic conditions in the countries of southern Europe. Another Swedish study, which documents the decline in attack rate for travel to southern Europe from one in 3000 unprophylaxed travelers in 1970-1972 to one in 20,000 unprophylaxed travelers in 1982, does not show such a decline in the risk of travel to Northern Africa, Tropical Africa and Asia. In 1982, the attack rates were one in 525, 95 and 144 unprophylaxed travelers to these regions, respectively(31).

A study of unprophylaxed Danish travelers between the years 1976-1978 revealed a higher attack rate (primarily of hepatitis A) in individual travelers to endemic regions than in travelers in tourist groups(32). Attack rates, extrapolated to cases per 100,000 airline travelers, ranged from 0.3 in individual travelers to northern and central Europe to 1482 cases per 100,000 airline travelers to Central Africa. Other areas of risk, in decreasing order, were Central and South America (740.7), North Africa (238.1), Asia (105.2) and the Middle East, excepting Israel, (86.1)Attack rates were remarkably lower in group travelers, ranging from 32.5 and 10.3 per 100,000 travelers to North and Central Africa, respectively, to zero cases for most other regions. A study by Steffen et. al. (28) in unprophylaxed Swiss travelers, demonstrated an incidence of 155 cases per 100,000 traveler-months abroad but identified no subpopulation with specific travel characteristics (such as age, destination, purpose, length and type of travel) that had increased or decreased incidence.

ISIG Prophylaxis

Documentation of Effectiveness

The effectiveness of immune serum immunoglobulin (ISIG) injections prior to work or travel in developing countries has been demonstrated in several studies few of which have been strictly controlled and double-blinded. Often quoted is Woodson's(33) comparison of unprophylaxed Protestant missionaries with routinely prophylaxed Peace Corps volunteers, revealing a rate of 3.0 icteric cases and 0.97 icteric or icteric cases per 100 person-years in the two groups, respectively. A 1969 British study showed a seven month incidence of 0.93 and 8.5 cases per 1000 prophylaxed and unprophylaxed relief workers, respectively(34). This study also showed that the effectiveness of ISIG waned after 7 months. Likewise, a truly controlled double-blinded study of American soldiers in Korea revealed 20 cases of hepatitis A in approximately 30,000 soldiers who had received ISIG within the past six months as opposed to 43 cases in approximately 20,000 soldiers who had not received ISIG, but the statistically significant differences between the two groups disappeared after six months(35). Since double-blind, controlled clinical trials of the effectiveness of ISIG prophylaxis in travelers to developing nations have not been performed, current CDC recommendations are based primarily on these studies in supposedly similar populations.

CDC Recommendations

These recommendations call for the intramuscular injection of 0.02 mL/kg ISIG for travelers who will be in developing nations for three months and 0.06 mL/kg every five months for extended-stay travelers(48). The classification of countries as "developing" is left ot the clinician, but extra caution is urged if patients are likely to be traveling in rural regions or are likely to be living in rustic accomodations.

Aside from limitation of exposure and administration of ISIG, the CDC also presents the possibility of serologically testing certain people whom the clinician feels might be immune, in order to avoid unnecessary injections of ISIG. The CDC handbook does not, however, provide an indication on what types of people might be tested.

Serological Screening for Immune Status of Certain Subgroups of the Travel Population as an Alternative to Routine ISIG Prophylaxis

Indeed, although ISIG prophylaxis is effective, there are several considerations which might make a serological search for immune individuals a desirable alternative to routine ISIG injections. Although the safety of intramuscular ISIG is well-documented, there are conditions in which safety might be of significant concern to the patient, if quantitatively only of minor concern to the clinician. The cost of ISIG is currently low enough to make serological screening cost-effective to patient or provider in only a very restricted set of circumstances. However, there are situations in which cost of ISIG may become a greater impetus for serological screening. Finally, there are conditions in which determination of immunity would be a very convenient alternative to ISIG

prophylaxis, although it would be difficult to quantify the benefits gained by serological screening. All of these factors which might make serological screening for immunity a desirable alternative to routine ISIG prophylaxis will now be reviewed.

Issues of Safety of ISIG Prophylaxis

Intramuscular administration of ISIG is a safe, as well as effective procedure, and adverse effects are primarily anecdotal. There have been reports of non-fatal anaphylaxis but these are extremely rare(45). The concern over the possible transmission of infectious agents, particularly human immunodeficiency virus (HIV), has been carefully studied. Several patients who received ISIG containing antibodies to HIV (collected before screening of donors was possible) were found subsequently to have positive ELISA and Western blot tests, but in all of these patients, the tests became negative after six months, suggesting that antibody, but not virus, had been transferred(36,37,38). Indeed, a study of the cold ethanol fractionation procedure used for ISIG production calculated the effectiveness of virus removal to be $1X10^{i5}$ *in vitro* infectious units per mL (IVIU/mL) for all of the steps combined(39). Since 1000 units of screened blood (the usual quantity for the preparation of a batch of ISIG) has been calculated to have a total of 0.13 IVIU/mL, the reduction of viral titer of 10^{i5} could be expected to produce a very safe product, and no cases of persistent seroconversion to anti-HIV positivity have been attributed to ISIG administration(40).

Nevertheless, particularly in those travelers who may require a second ISIG injection while in a developing country, where blood may not be

screened, where quality control is limited(41), and where needles may not be new, prior determination of HAV status may reduce risk by enabling immune individuals to avoid unnecessary injections.

Issues of Cost of ISIG Prophylaxis

Financial incentives for screening are not compelling but depend on testing philosophy and differ for patient and provider. For example, the cost in 1990 of 2 mL of ISIG to the patient at Yale-New Haven Hospital (YNHH) is $18.00. In comparison, the hospital charges $20.00 for the anti-HAV IgG ELISA. Hospital policy requires an anti-HAV IgM ELISA for all positive IgG tests, and charges the patient an additional $20.)) for this test. Under such circumstances, an immune patient only saves money if he or she has a 100% chance of immunity and will require more than two ISIG injections, a condition which would obtain in repeat or extended-stay travelers. If the hospital did not require an anti-HAV IgM test for obviously healthy pretravel patients with a positive anti-HAV IgG test, then an immune patient saves money if he or she would have required more than one ISIG injection.

A provider's considerations are somewhat different, based on costs to YNHH. One dose of ISIG costs $2.00, the anti-HAV IgG ELISA costs $4.00 and the anti-HAV IgM ELISA costs $10.00. If the provider insists on an IgM test after a positive IgG test, then it saves money if a known immune individual would have required seven ISIG injections. If the requirement for the second IgM test is waived, then the provider saves money if an immune individual would have required two ISIG injections. Clearly, so long as the present ratio of ISIG administration to HAV test cost remains

low, cost alone is not a strong impetus for screening except in frequent travelers. Indeed, cost minimization strategies in the U.S. are currently not very sensitive to the prevalence of immunity in target populations. It is conceivable, however, that ISIG could become more expensive if, for example, supplies became limited. The recent shortage of ISIG due to large military requirements might provide an added incentive for screening.

Suitable criteria for screening might also be important when a vaccine for HAV becomes available, since cost will probably initially be a greater issue than with ISIG prophylaxis. A recent trial of killed HAV vaccine produced antibodies at levels higher than those obtained with ISIG, and which persisted for 24 weeks. Further studies will determine if such a vaccine will soon be available(43).

Issues of Convenience of ISIG Prophylaxis

Another situation in which it might be convenient to know anti-HAV antibody status is in those patients who also require revaccination for measles before travel (ie. those vaccinated before 1980). Because ISIG interferes with development of active immunity to measles, the vaccine should not be given for at least six weeks, and preferably for three months after ISIG injection. Conversely, ISIG should not be given less than 14 days after a measles vaccine because 7-10 days is required for immune stimulation. Pretravel preparation might not allow for the maintenance of such intervals. Thus, identifying HAV immune individuals among those travelers also needing the measles vaccine might obviate the

need for untimely ISIG administration which, in turn, would require a repeat measles vaccine or a check of measles serology(42).

British Studies Assessing Criteria for a Cost-Effective Approach to Serological Testing

In Great Britain, which has a nationalized health service, the desire of the health care provider to reduce costs has led to an interest in determination of screening criteria. According to one British study(44), ISIG costs 8.00 per administration while a salivary anti-HAV IgG capture immunoassay costs 4.00. Thus, total cost will be quite sensitive to the prevalence of immunity in those tested. These investigators found a prevalence of immunity ranging from 27% in the >20 year old age group to 45% in the >50 year old age group. Prevalence in those with Asian surnames was 72% and was 74% in those with a history of jaundice. Assuming the listed costs of ISIG and the salivary test, considering the average individual lifetime requirement of ISIG to be 1.25 injections, and taking into account the expected age, racial composition and medical history of 1000 random subjects (in whom the total HAV prevalence would be expected to be 26%), these authors calculated a minimization of cost if the following groups were tested: 1), frequent or long-stay travelers >30 years old 2), travelers >60 years old 3), travelers born in countries of high HAV prevalence and 4), travelers with a history of jaundice. Costs could be maintained at current levels while at the same time minimizing ISIG injections in immune patients by testing patients with the following criteria: 1) travelers >40 years old, 2), extended - stay travelers, 3), travelers born in countries of high HAV prevalence and 4), travelers with a history of jaundice.

A more recent study(45) of travelers at an inner-city travel clinic in London demonstrated an HAV prevalence of 42% in 104 consecutive travelers tested. Of these immune individuals, 61% had been born or raised in HAV endemic regions or had a history of jaundice (classified as major risk factors) while 27% had a history of drug abuse, living in a squat or traveling rough, or of living with someone who had had jaundice (classified as minor risk factors). Altogether, 48% of those tested who had minor risk factors were immune, while 100% of those with major risk factors were immune. However, in this population, 10% of patients with no risk factor were immune.

Design of This Study to Determine Factors in Past Medical and Travel History Associated with Hepatitis A Immunity

The purpose of this study was to determine which factors in the past medical and travel history of U.S. travelers would be associated with hepatitis A immunity, and to measure the overall prevalence of immunity in the travel clinic population. The results from this study would assist clinicians in deciding whom to test for immunity.As the prevalence of HAV immunity in the travel clinic was determined to be small, it was decided to do a case-control study(46). Such a study would not allow for a quantitative assessment of risk factors and would not provide the information necessary to design a cost-effective strategy for testing. Nevertheless, it might provide the basis for studies which could obtain such information if cost or other factors rendered quantitative analysis more clearly useful.

Given the constraints of the extant database, only certain factors could be explored. It seemed probable that, as in the study of Parry et. al.(44),

hepatitis A immunity would be associated with greater age and with a history of hepatitis. Although surnames cannot be used in the U.S. to predict with great accuracy one's origin, birth or upbringing in a developing country would likely be associated with hepatitis A immunity. Furthermore, previous travel to developing nations, especially without evidence of hepatitis A prophylaxis might be associated with hepatitis A immunity, since such travel would a connote a risk above that of the general population. Gender, on the other hand, would not be expected to correlate with hepatitis A immunity. Unfortunately, socioeconomic status of patients could not be assessed, although travel itself, and attendance at largely self-pay travel clinics connotes a certain socioeconomic status.

Although these factors are not necessarily independent (eg. older people have had more time in which they might have traveled abroad), within the context of the already self-selected population that comes to a travel clinic, they may provide the clinician with extra impetus to immunologically screen. Likewise, certain aspects of patients' travel intentions might prove reflective of factors in their past which are predictive of hepatitis A immunity. Thus, intended destination, purpose and length of travel were recorded.

Methods

Patients who attended the Yale Tropical Medicine and Traveler's Clinic(YTC) or the Yale University Health Services travel clinic(YHP) between January 1987 and September 1990 for pretravel counsel and immunizations were routinely tested for anti-HAV IgG antibodies in their serum. One of the travel clinic physicians(J.P.) claimed to have tested a preponderance of older patients while another physician(M.B.) reported testing all travel clinic patients coming for pretravel evaluation. Potential distinguishing factors in the subjects tested by two other travel clinic physicians are not known. The serological test used was the HAVAB Enzyme Immunoassay Kit produced by Abbott Laboratories. Patients were also questioned about various aspects of their past medical and travel history and responses were generally recorded in a standardized form. If time permitted, patients would return to the clinic just prior to travel for ISIG administration if they were found not to be immune, otherwise they would receive ISIG without waiting for the results of serological testing.

Beginning in Spring, 1990, logbooks were reviewed manually or by computer search to find the unit numbers or the names of immune and non-immune patients. Identification of the birthdates of nearly all of those tested provided data on HAV prevalence in different age-groups. The charts of patients at the Yale Travel Clinic were checked and the

data concerning their past medical and travel history were collected. Specifically, age, gender, birthplace, current travel plans at time of visit, reason for travel, length of intended stay, and past history of hepatitis and previous travel were reviewed. Patients whose charts were incomplete were contacted by mail and invited to fill out a written questionnaire or provide responses over the telephone. Because the charts of YHP travel clinic patients were unavailable, mailed questionnaires were used to obtain information on their medical and travel history.

Although contact with all non-immune patients was not attempted, subjects were chosen randomly to provide a 2:1 ratio of controls to cases. The names of several non-immune subjects listed on either side of those of immune subjects in the logbooks or computer printouts were selected. Because there was a greater number of non-immune subjects available for study, non-immune subjects with incomplete charts were not pursued, instead, the completed charts of other non-immune subjects would be selected. Collection and treatment of data proceeded according to the regulations of Protocol #5612 of the Human Investigation Committee of Yale University School of Medicine and the of the Yale University Health Services.

Results were tallied and responses for various aspects of medical and travel history in immune and non-immune subjects were compared. Differences in the percentages of immune cases and non-immune controls with certain factors were tested for statistical significance by computing a chi-squared value and interpreting this with one degree of freedom to find the two-tailed p value. If the number of subjects included in a test for statistical significance was less than 150 or if the p value was

greater than 0.005, the Yates continuity correction was used. Odds ratios and the associated 95% confidence intervals were also calculated. The Mantel-Haenzel tests for confounding and effect modification were performed where possible.

Results

Results of Age-Prevalence Study

HAV-Immune subjects/Total subjects in group(%)

Age-group(years)

	0-9	10-19	20-29	30-39	40-49	50-59	60-69	>70	Total
YHP	0/7(0)	0/1(0)	5/73(7)	10/43(23)	4/24(17)	1/9(11)	7/18(39)	7/8(88)	43/183(19)
YTC	0/4(0)	0/20(0)	9/112(8)	13(119)11	14/79(18)	14/82(17)	14/53(26)	7/24(29)	71(493(14)
Tot.	0/11(0)	0/21(0)	14/185(8)	23/162(14)	18/103(17)	15/91(16)	21/71(30)	14/32(44)	105/676(16)

(YHP signifies Yale University Health Services and YTC signifies Yale Tropical Medicine and International Traveler's Clinic)

HAV-Immune Subjects/Total Subjects in Group(%)

Age-Group(yrs.)	YHP	YTC	Total
>10	34/176(19)	71/489(15)	105/665(16)
>20	34/175(19)	71/469(15)	105/644(16)
>30	29/102(28)	62/357(17)	91/459(20)
>40	19/59(32)	49/238(21)	68/297(23)
>50	15/35(43)	35/159(22)	50/194(26)
>60	14/26(54)	21/77(27)	35/103(34)

Results of Case-Control Study

DESCRIPTION OF SUBJECTS

	Immune	Non-immune
Total	62	121
Mean Age(range)	53(18-81)	38(17-71)
Males(%)	27(44)	63(52)
Females(%)	35(56)	58(48)

AGE

Subjects(% of subjects in row)

Age-Group(years)	0-19	20-29	30-39	40-49	50-59	60-69	>70	Total
Immune	1(2)	3(5)	9(15)	12(19)	12(19)	18(29)	7(11)	62
Non-immune	2(2)	35(29)	34(28)	21(17)	18(15)	10(8)	1(1)	121
Total	3(2)	38(21)	43(23)	33(18)	30(16)	28(15)	8(4)	183

GENDER

Subjects(% of subjects in that row)

	Male	Female	Total	
Immune	27(44)	35(56)	62	
Non-immune	63(52)	58(48)	121	
Total	90(49)	93(51)	183	p>0.25 NS

HISTORY OF HEPATITIS

Subjects(% of subjects in that row)

	History of Hepatitis	No History of Hepatitis	Total
Immune	20(32)	42(68)	62
Non-immune	2(2)	119(98)	121
Total	22(12)	161(88)	183
			p<.001

PLACE OF BIRTH

Subjects(% of subjects in that row)

	Born in U.S.	Not Born in U.S.	Total	
Immune	40(65)	22(35)	62	
Non-immune	107(88)	14(12)	121	
Total	147(80)	36(20)	183	p<.001

Breakdown of Place of Birth--Immune Subjects

Region or Country	Number of Subjects	
Ghana	2	
Bangladesh	2	
India	2	
Egypt	1	
Israel	1	
Vietnam	1	
Thailand	1	
Argentina	1	
Chile	1	
W. Europe	9	(Germany-1,Italy-3, Britain-2, Austria-1, France-1)
Not U.S. (not otherwise specified)	1	

Breakdown of place of birth--Non-immune subjects

Region or Country	Number of Subjects	
Libya	1	
Israel	1	
Curacao	1	
Japan	2	
W. Europe	2	(Netherlands-1, Norway-1)
Canada	1	
Not U.S. (Not otherwise specified)	6	

PROFILE OF DESTINATIONS OF TRAVELERS

Immune Subjects:

Number of responses(% of subjects). Percentages will sum to greater than 100% due to multiple responses from some subjects.

South/Central America	N. Africa	Other Africa	S.E. Asia	Other
11(18)	7(11)	30(48)	10(16)	11(18)

Country or Region	Number of Subjects
Kenya	8
Tanzania	6
India	5
Egypt	4
Ghana	4
Mexico	4
Thailand	3
Peru	3
China	2
Senegambia	2
Nepal	2
Zimbabwe	2
Honduras	1

Mentioned once:

Philippines, Taiwan, Singapore, New Guinea, HongKong, Bali, S.E. Asia, Bangladesh, Pakistan, Mali, Cameroon, Morocco, Mauritania, N.W. Africa, Burundi, Mozambique, Liberia, Tunisia, S. Africa, Central African Republic, Brazil, Uruguay

Non-immune Subjects

Number of Responses(% of subjects). Percentages will sum to greater than 100% due to multiple responses from some subjects.

South/Central America	N. Africa	Other Africa	S.E. Asia	Other Asia
44(36)	6(5)	54(45)	16(13)	39(32)

Region or Country	Number of Subjects
India	20
Kenya	19
Nepal	11
Brazil	10
Tanzania	10
Galapagos	6
Zimbabwe	5
Thailand	5
Peru	5
Haiti	4
South Africa	3
Egypt	3
Singapore	3
Liberia	3
Belize	3
Guatemala	3
Nicaragua	2
Costa Rica	2
Sri Lanka	2
Dominican Republic	2
Japan	2
Morocco	2
Senegal	2
Togo	2
Venezuala	2
Central Asia	2

Mentioned once:

Mali, Ivory Coast, Ethiopia, Zaire, Cameroon, Burundi, Zambia, N.W. Africa, Nigeria, Uganda, Botswana, Mauritania, Guyana, Ecuador, Mexico, Honduras, Argentina, S. Asia, Malaysia, Philippines, Hong Kong, Pakistan, Vietnam, Cambodia, Hawaii, Bhutan, Saudi Arabia, Israel

COMPARISON OF PROJECTED LENGTH OF TRAVEL

Subjects(% of total of that row)

	less than or equal to 3 wks.	>3wks.<1yr.	>1yr.	Not Mentioned	Total
Immune	37(60)	17(27)	3(5)	5(8)	62
Non-immune	66(55)	50(41)	5(4)	0(0)	121

Comparison of Purpose of Travel

Responses(% of subjects in that group)
(Percentages sum to greater than 100% because of multiple responses from some subjects)

	Business	Volunteer Wk.	Study	Tourist	Visit Relative	Field Wk.	Not Mentioned	Sub.
Immune	8(13)	9(15)	1(2)	32(52)	6(10)	3(5)	5(8)	62
Non-Immune	14(11)	23(19)	10(8)	70(57)	3(2)	2(2)	0(0)	121
Total	22(12)	32(17)	11(6)	102(55)	9(5)	5(3)	5(3)	183

Continent of previous developing nation travel

Responses(% of subjects in that row)
(% may add up to greater than 100% due to multiple responses from some subjects)

	Asia	South/Central America	Africa	Other	None
Immune	25(40)	17(27)	23(37)	2(3)	8(13)
Non-immune	47(39)	31(26)	29(24)	1(1)	46(38)

Number of subjects with history of previous developing nation travel with history of associated immunization (not necessarily ISIG)

Subjects(% of subjects with previous developing nation travel)

	Some evidence of previous pretravel care	No evidence, or denial of previous pretravel care	Total	
Immune	27(50)	27(50)	54	
Non-immune	24(32)	51(68)	75	p>.05 NS

Evidence of previous pre-travel care included recollection of previous pre-travel immunizations or records of previous pre-travel visits or

immunizations in medical charts. In the other category were placed subjects who denied previous pre-travel medical care or whose medical charts contained no evidence of previous pre-travel visits. Patients who had had pre-travel visits for some but not all trips to developing nations were entered as having evidence of previous pre-travel medical care.

Statistical Analysis

I. Age-Prevalence Study in YHP and YTC Populations

The overall prevalence of HAV immunity in the YHP and YTC populations was 19% and 14%, respectively. To test if this difference between the two populations was statistically significant, a 2x2 table was constructed, with clinic source as the "risk factor" and the number of subjects in each category entered into the appropriate cells.

	immune	non-immune
YHP	34 (a)	149 (b)
YTC	71 (c)	422 (d)

A simplified form of the equation for chi square is:

$$\chi^2 = \frac{(ad-bc)^2 N}{(a+b)(c+d)(a+c)(b+d)}$$

where cells are as labelled above, and N=a+b+c+d. Thus:

$$\chi^2 = \frac{(34\cdot422 - 71\cdot149)^2 676}{(34+149)(71+422)(34+71)(149+422)} = 1.78$$

At one degree of freedom (df), p(two-tailed)>0.10, signifying that there is a greater than 10% probability that this difference arose by chance. (All p values subsequently presented will be two-tailed and interpreted at 1 df).

The differences in prevalences between similar age-groups in the two populations were also checked separately for statistical significance.

30-39 year-olds

	immune	non-immune
YHP	10	33
YTC	13	106

Yates' continuity correction is used:

$$\chi_c^2 = \frac{(|ad-bc| - N/2)^2 N}{(a+b)(c+d)(a+c)(b+d)}$$

$$= \frac{(|10\cdot106 - 33\cdot13| - \frac{162}{2})^2 162}{(10+33)(13+106)(10+13)(33+106)} = 3.0$$

$p > 0.05$ Not significant (NS)

59 -olds

	immune	non-immune
YHP	1	8
YTC	14	68

tes' Continuity correction used for small sample size

$$\chi_c^2 = \frac{(|11.68 - 14.81| - \frac{91}{2})^2 91}{(1+8)(14+68)(1+14)(8+68)} = 0.21$$

$$P > 0.50 \quad NS$$

60-69 year-olds

	immune	non-immune
YHP	7	11
YTC	14	39

$$\chi_c^2 = \frac{(|17.39 - 14.11| - \frac{71}{2})^2 71}{(7+11)(14+39)(7+14)(11+39)} = 0.49$$

$$P > 0.25 \quad NS$$

See Conclusions for discussion of these results.

II. Case-Control Study

A. Analysis of the different age-groups amongst the cases and controls.

Age	immune	non-immune
≥20 yrs.	61 (a)	119 (b)
<20 yrs	1 (c)	2 (d)

The odds ratio (or, the ratio of the likelihood that immune subjects will have exposure to the "risk factor" to the likelihood that non-immune subjects will have such exposure) is determined by the following formula:

$$\text{Odds ratio (OR)} = \frac{a/c}{b/d} = \frac{ad}{bc} = \frac{61 \cdot 2}{119 \cdot 1} = 1 \cdot 03$$

$$\chi^2 = \frac{(61 \cdot 2 - 1 \cdot 119)^2 183}{(61+119)(1+2)(61+1)(119+2)} = 0 \cdot 23$$

$p > 0 \cdot 50$ NS

Age

	immune	non-immune
≥ 30 years	58	84
< 30 years	4	37

OR = 6·4
χ^2 = 13·7
$p < 0 \cdot 001$

The 95% Confidence Interval (95% CI) of an odds ratio is calculated according to the formula:

$$95\%\ CI = OR^{1 \pm 1 \cdot 96/\chi}$$

Thus:

$$95\%\ CI = 6 \cdot 4^{1 \pm 1 \cdot 96/3 \cdot 7} = 2 \cdot 4 \text{ to } 7 \cdot 1$$

Age

	immune	non-immune
≥40 yrs.	49	50
<40 yrs.	13	71

OR = 5·3
χ^2 = 23·5
$p < 0 \cdot 001$
95% CI = 2·7 to 10·4

Age

	immune	non-immune
≥50 yrs	37	29
<50 yrs	25	92

OR = 4·7
χ^2 = 22·7
$p < 0 \cdot 001$
95% CI = 2·5 to 8·9

	immune	non-immune
≥60 yrs.	25	11
<60 yrs.	37	110

$OR = 6.8$
$\chi^2 = 25.3$
$p < 0.001$
95% CI = 3.2 to 14.4

The association of increased age with immunity may be due to the confounding effects of the increased opportunity of older people already to have had previous travel to developing nations and to already have had hepatitis. A confounding factor must be independently associated with exposure (here, increased age), outcome (immunity), and not lie on the causal pathway from exposure to outcome. One way to control for confounding is by stratification of the odds ratios by previous travel and by previous hepatitis status, and to calculate the Mantel-Haenzel odds ratio. The Mantel-Haenzel(MH) analysis requires categorical variables and so age-groups have been stratified into >40 year-olds and <40 year olds for this and all subsequent MH analyses. Assessing for the effect of previous travel:

	immune	non-immune
≥40 yrs.	42	33
<40 yrs.	12	42

$OR = 4.5$

no previous travel

	immune	non-immune
≥40 yrs.	7	17
<40 yrs.	1	29

$OR = 11.9$

$$OR_{Mantel\text{-}Haenzel} = OR_{MH} = \frac{\sum a_i d_i / N_i}{\sum b_i c_i / N_i}$$

where $N_i = a_i + b_i + c_i + d_i$

$$OR_{MH} = \frac{(42 \cdot 42)/129 + (7 \cdot 29)/54}{(12 \cdot 33)/129 + (1 \cdot 17)/54} = 5.2$$

These results will be discussed in the Conclusions section. The possible confounding effects of hepatitis in older subjects cannot be assessed by the MH procedure because one of the cells has a value of zero. However, one can check if age and hepatitis could be associated by comparing the average age of immune subjects with a hepatitis history with the average age of those without such a history. If the former group were much younger than the latter, then it would appear that hepatitis and increased age were not associated. Since the approximate age of both groups is approximately 53 years old, one

cannot rule out the possibility that increased age and hepatitis history are associated and therefore, may be confounding each other's association with HAV immunity.

B. Gender

	Immune	Non-immune
Male	27	63
Female	35	58

OR = 0.71
$\chi^2 = 1.19$
$p > 0.25$ NS
95% CI = 0.38 to 1.3 (NS)

C. Place of Birth

An attempt is made in the Conclusions section to distinguish foreign-born (developed and developing countries) and U.S. born populations on the basis of average age. The two-sample t-test was used to determine statistical significance of the differences between two means. Thus:

Immune subjects

	U.S. born (n=40)	foreign-born (n=22)
$\bar{x}$ (yrs.)	57.3	45.5
σ (yrs.)	15.0	12.3

where $\bar{X} = \frac{\Sigma x_i}{N}$

and $\sigma = \sqrt{\frac{\Sigma (x_i - x)^2}{n-1}}$

$$= \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{S_p^2 \left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

where $S_p^2 = \frac{(n_1-1)\sigma_1^2 + (n_2-1)\sigma_2^2}{n_1 + n_2 - 2}$

$t = 3.15$ $p < 0.005$

Non-immune subjects

	U.S. born (n=107)	foreign-born (n=14)
(yrs.)	38.4	38.4
(yrs)	13.4	11.8

t-test not performed because mean age's were the same

Foreign-born immune individuals

	Developing countries (n=12)	Developed countries (n=9)	Not mentioned (n=1)
(yrs)	39.1	55.6	-
(yrs.)	8.7	9.4	-

$t = 4.46$ $p < 0.001$

Foreign-born non-immune individuals	Developing countries (n=3)	Developed countries (n=5)	Not mentioned (n=6)
.)	27.0	36.2	-
)	1.4	6.8	-

$t = 2.58 \quad p < 0.05$

	immune	non-immune
foreign-born	22	14
U.S.-born	40	107

OR = 4.2
$\chi^2 = 14.8$
$p < 0.001$
95% CI = 2.0 to 8.7

An MH analysis was used to assess the confounding effects of previous travel to developing nations and of a hepatitis history in the association of immunity and foreign birth. (N.B. Small cell numbers may lessen the validity of some of these analyses). Effect of previous travel:

	immune	non-immune
foreign-born	20	11
U.S.-born	34	64

OR = 3.4

OR_{MH} = 3.6

no previous travel

	immune	non-immune
foreign-born	2	3
U.S.-born	6	43

OR = 4.8

As the OR_{MH} is approaching unity, a second test for statisitical significance must be performed using a weighted Mantel-Haenzel chi square calculated according to the formula:

$$\chi^2_{MH} = \left(\sum \frac{a_i d_i - b_i c_i}{N_i} \right)^2 \Big/ \sum \frac{r_{1i} r_{2i} c_{1i} c_{2i}}{(N_i - 1)(N_i)^2}$$

a_i, b_i, c_i, d_i = cell values of the i^{th} stratum; $N_i = a_i + b_i + c_i + d_i$

and $r_{1i} = a_i + b_i$; $r_{2i} = c_i + d_i$; $c_{1i} = a_i + c_i$; $c_{2i} = b_i + d_i$

so

$$\chi^2_{MH} = \frac{\left[\frac{(20 \cdot 64 - 34 \cdot 11)}{129} + \frac{(2 \cdot 43 - 6 \cdot 3)}{54} \right]^2}{\frac{31.98 \cdot 54.75}{(129-1)(129)^2} + \frac{5.49 \cdot 8.46}{(54-1)(54)^2}} = 10.8$$

$p < 0.01$

95% CI of $OR_{MH} = 3.6^{1 \pm 1.96/3.3} = 1.7$ to 7.7

Effect of a hepatitis history

	immune	non-immune
foreign-born	5	1
U.S.-born	15	1

OR = 0.33

⊕ hepatitis history

	immune	non-immune
foreign-born	17	13
U.S.-born	25	106

OR = 5.5

OR_{MH} = 4.2

D. Hepatitis History

	immune	non-immune
⊕ hepatitis history	20	2
no hepatitis history	42	119

OR = 28.3
χ^2 = 36.3
$p < 0.001$
95% CI = 9.5 to 84.3

For a hepatitis history, there are several possible confounding factors.

1. Patients with a history of hepatitis may be older and for this reason may be more likely to be found amongst immune patients.
2. Patients with a history of hepatitis may be more likely to have a history of previous travel to developing nations and for this reason may be more likely to be found amongst immune patients.
3. Patients with a history of hepatitis may be more likely to have been born outside of the U.S. and for this reason may be more likely to be found amongst immune patients.

The first two of these possibilities are not amenable to MH analysis because of zero subjects in some cells. However, it has been shown in the analysis of age that hepatitis history and age cannot be shown not to be associated. Applying MH analysis to the third possibility:

	immune	non-immune
⊕ hepatitis history	5	1
no hepatitis history	17	13

OR = 3.8

OR_{MH} = 19.6

U.S.-born

	immune	non-immune
⊕ hepatitis history	15	1
no hepatitis history	25	106

OR = 64

E. Previous Travel

	immune	non-immune
previous travel	54	75
no previous travel	8	46

OR = 4.1
χ^2 = 12.4
$p < 0.001$
95% CI = 1.9 to 9.1

Assessment of the possible confounding effect of hepatitis could not be done because of zero subjects in some cells. Assessment of confounding effect of greater age:

	immune	non-immune
⊕ previous travel	42	33
no previous travel	7	17

OR = 3·1

Age < 40yrs

	immune	non-immune
⊕ previous travel	12	42
no previous travel	1	29

OR = 8·3

$OR_{MH} = 4.0$

Assessment of the confounding effect of foreign birth:

	immune	non-immune
⊕ previous travel	20	11
no previous travel	2	3

OR = 2·7

U.S.-born

	immune	non-immune
⊕ previous travel	34	64
no previous travel	6	43

OR = 3·8

$OR_{MH} = 3.6$

$$\chi^2_{MH} = \frac{\left[\frac{(20\cdot3 - 2\cdot11)}{36} + \frac{(34.43 - 6.64)}{147}\right]^2}{\frac{31\cdot5 \cdot 22.14}{(36-1)(36)^2} + \frac{92\cdot49.40\cdot107}{(147-1)(147)^2}} = 9.3$$

$p < 0.01$

95% CI of OR_{MH} = 1·6 to 8·3

F. Expected Destinations of travelers not assessed statistically.

G. Expected Length of Travel (disregarding subjects with unspecified lengths of travel):

	immune	non-immune
≤ 3 wks	37	66
> 3 wks	20	55

OR = 1·54
$\chi^2 = 1.7$
$p > 0.10$ NS
95% CI = 0·8 to 2·9 NS

H. Purpose of Travel not assessed statistically.

I. Subjects with a history of previous travel to developing nations who give a history of associated immunizations:

	immune	non-immune
evidence of previous pretravel care	27	24
no evidence of previous pretravel care	27	51

OR = 2·1
$\chi^2_c = 3.6$
$p > 0.05$ NS
95% CI = 1·4 to 3·1

Discussion

Prevalence of HAV immunity was 19% and 14% in the YHP and YTC populations, respectively, with an increasing prevalence with increasing age. In the case-control aspect of the study, immune individuals were found more likely than non-immune individuals to be older, to have traveled previously, to have been born outside of the U.S. or to have a history of hepatitis. Mantel-Haenzel (MH) analysis was performed where possible to determine the importance of confounding and effect-modification in the associations between these factors and HAV immunity. No other factors were found to be associated with HAV immunity. Various biases were assessed and considered to be of limited significance in this study.

General Prevalence

As the differences between the YHP and YTC populations were determined not to be statistically significant ($p>0.05$), it was decided to pool the results from the two groups, although incurring a Type II error in so doing was certainly a possibility.The prevalence of HAV immunity in the combined groups was 15.5%, which is lower than the 26% and 42% reported for two British travel clinic populations(44,45). The prevalence was also lower than that reported in an American middle-class population in 1976(15,16). Because ours was a case-control study, however, the proportions of other subgroups in the two populations (such as individuals born outside the host country or individuals with a history of hepatitis) could not be compared. Likewise, a comparison of our group with that of Szmuness et. al.(15) is not possible. Nevertheless, one could speculate that our

group came from a higher socioeconomic background than did those from the previous American study and from the British inner-city study(45).(Indeed, it is unlikely that 10% of our travel population had a history of drug abuse, living in a squat or traveling rough, as was the case in that British study).Another possible explanation for a lower prevalence of HAV immunity in our study could be a reduced prevalence in the population as a whole as compared with those in Britain or those in the U.S. in the 1970's. Finally, it should be remarked that in the study of Parry et. al.(44), a conscious effort was made to test a population likely to have a higher prevalence of HAV immunity, though the degree to which this overestimated the prevalence of the population as a whole is not clear. It is interesting to note that very little work on the prevalence of HAV immunity in the U.S. has been done since the 1970's, although it is not certain that revelation of any changes would be very useful since the incidence of hepatitis A is currently very low and since outbreaks usually have well-recognized sources.

Age Factor and Hepatitis A Immunity

The increasing prevalence with increasing age was expected. Older patients have had more time in which to be exposed to HAV and to develop lifelong immunity. Furthermore, seroepidemiologic data from the developed nations suggest that it is within the past 50-75 years that hygienic standards progressed to a point capable of reducing incidence of hepatitis A, and so, older patients have lived in time periods when incidence was higher than it is now(22,23).

An analysis of the age profiles of the case-control study groups reflects the increased prevalence with increased age by demonstrating

a greater likelihood that immune individuals will be older than a certain age than their non-immune controls will be. The only age cut-off where such a likelihood is not statistically significant is 20 years old. The odds ratios do not follow an explicable pattern but statistical significance is greatest for the age cut-off of 60 years where it is seen that immune individuals are 6.8 times more likely to be over 60 years old than are their non-immune counterparts.

The possible confounding effect of previous travel to developing nations and of a hepatitis history was assessed because older patients may have had more time to experience either of these potential factors than younger patients will have had, and these factors may be independently associated with immunity. Stratifying the >40 and <40 year-old age-groups by presence or absence of previous travel did not reduce the MH odds ratio, and so the greater odds of older people being found among immune individuals is not due to the greater possibility that they will have traveled previously. On the other hand, there is striking effect modification, wherein it is seen that immune subjects with a history of previous travel have a less increased likelihood(OR=4.5) to be found to be older than immune subjects without such a history(OR=11.9), suggesting that age and previous travel are independently associated with immunity. (Ie. if one factor accounts for a subject's immunity, then the other does not). Alternatively, if one considers odds ratios to be equivalent to risk ratios (which can be done for low-prevalence outcomes), the presence of previous travel reduces the relative risk of older age "causing" immunity. What this means biologically is not clear, however, the presence of effect modification informs the clinician that increased

age will be a more important predictive factor for immunity in patients without a history of previous travel to developing nations than in those with such a history. The possibility that an older person will have had more time to contract hepatitis and that this accounts for the increased odds of finding older people among immunes could not be checked by the MH procedure, and calculation of average ages demonstrated that an association of age and hepatitis cannot be ruled out. (Note that such an association between age and symptomatic hepatitis presumably accounts for only part of the increased prevalence of immunity in older people, as one expects many of these older people to have developed immunity when hepatitis A was an endemic disease and therefore, more likely to express itself in asymptomatic form. Indeed, to be a true confounder, cases of symptomatic hepatitis cannot be a result of increased age).

Gender Factor and Hepatitis A Immunity

Gender was shown not to bear a statistically significant relationship to immunity. Although immune individuals were only 0.71 times as likely to be males as were their non-immune counterparts, the chi square value demonstrated that there was a greater than 25% probability that this discrepancy had occurred by chance. Furthermore, the 95% CI of the odds ratio (0.38 to 1.32) includes 1.0, which implies no added or reduced likelihood of immune individuals being male. It was not expected that immunity would be associated with one gender or another, since hepatitis A has no known sex predilection.

Place of Birth and Hepatitis A Immunity

Conversely, immune individuals were found to have a statistically significant 4.2 times greater probability of being born outside the U.S. than were non-immune individuals. This would imply that individuals born outside of the U.S. have a higher prevalence of immunity to hepatitis A, as was also suggested by the data of Szmuness et. al.(15). The mean ages of U.S. born and foreign-born immune subjects were 57.3 and 45.5, respectively($p<.005$) which suggests that age and foreign birth are independently associated with immunity. (Such a discrepancy in mean ages(38.4 years) between foreign and U.S.-born non-immune subjects did not exist, further supporting the independence of age and place of birth in determining immunity). An increased prevalence might be expected in those born in developing countries as well as in older patients born in countries which had a higher incidence than the U.S. years ago, but which may be considered developed countries now and which have a low incidence currently. Approximately one-half of the foreign-born individuals were from the developing countries while the rest were from western Europe. Their mean ages were 38.5 and 55.6 years, respectively,($p<.001$), which would seem to support such a distinction. (On the other hand, a discrepancy also existed between the mean ages of foreign-born non-immune subjects from developing and developed countries(27 and 36 years, respectively),although statistical significance was much less($p<.05$) and many foreign-born subjects had not provided a country of birth).

The possibility that foreign-born individuals were more likely to have previously traveled to developing nations, or to have had hepatitis, and

that either of these possibilities may have accounted for the increased odds of finding foreign-born subjects among immunes was subjected to MH analysis. Indeed, because more foreign-born individuals were likely to have traveled previously, the adjusted OR_{MH} of 3.6 was lower than the crude OR of 4.2. Nevertheless, one notes an effect-modification wherein immune subjects with a history of previous travel have a less-increased likelihood of being found to be foreign-born(OR=3.4) than those without previous travel(OR=4.8), suggesting that although foreign-born individuals are more likely to have had foreign travel, this does not account for their immunity. A hepatitis history is found not to be a confounding factor(OR_{MH}=4.2). Moreover, the effect modification shows that a hepatitis history and foreign birth are unlikely both to account for one's immunity. Again, considering odds ratios to be equivalent to risk ratios, one could conclude that foreign birth is a more useful predictive factor for immunity in those patients without a history of hepatitis or of previous developing nation travel than in those with such a history.

Hepatitis History and Hepatitis A Immunity

Immune individuals had 28.3 greater odds of having a history of hepatitis than did non-immune individuals. It would be expected that a past episode of hepatitis would be correlated with HAV immunity even if, as noted in previous studies(15,16), only 3-5% of HAV immune individuals will give a history of hepatitis. This study suggests that 32% of immune individuals can give such a history. This may signify that travel patients develop hepatitis A in a context in which it is more likely to be symptomatic or diagnosed, a possibility that would seem consistent with the expected higher socioeconomic status of travelers.

On the other hand, some of the patients with hepatitis were young and were born outside of the U.S. and so may have contracted hepatitis A in an endemic region.

It has been shown that a history of hepatitis and of increased age may be associated with each other, although the nature of this association is not demonstrable with these data. The possible association of previous travel and hepatitis history could not be assessed because of cells with zero subjects. The possible confounding effect of foreign-birth(associated with, but not causing a hepatitis history, and associated with immunity) was shown to be significant, as the OR_{MH} of 19.6 is markedly reduced from the crude OR of 28.3. Nevertheless, a history of hepatitis is still a very important factor associated with immunity and could be considered to be highly predictive of immunity, particularly in U.S. born patients.

Previous Travel and Hepatitis A Immunity

Previous travel to developing countries was expected to have some correlation with immunity.Even prophylaxed travelers from the U.S. have, according to the data of Woodson(33) and Conrad and Lemon(35), a 7-100-fold greater incidence of hepatitis A than individuals in the U.S.(17). The incidence is even greater for unprophylaxed travelers. Two of the twenty immune individuals with a history of hepatitis in this study had developed hepatitis during previous travel, although one of these cases occurred in France from eating raw seafood. Since most cases of travel hepatitis would occur in adults and thus, be symptomatic, it is surprising that despite the large percentage of immune travelers who had traveled to developing countries, only one of them could attribute immunity to that factor.

Nevertheless, immune subjects had a 4.1 times greater probability of previous travel to developing nations than did non-immune subjects. An MH analysis for confounding of the association of immunity and previous travel by hepatitis history was not done due to zero values in some cells. One might doubt the value of such an analysis anyways, because one would expect that most immunity secondary to previous travel would arise from symptomatic cases of hepatitis A (since most travelers are adults). If this were the case, a hepatitis history would lie along the causal path from exposure(travel) to outcome (immunity) and thus not fulfill the criteria for a confounding factor. Greater age is shown not to confound the association of previous travel with immunity(OR_{MH}=4.0 OR_{crude}=4.1), although a history of previous travel to developing nations is of greater predictive value in younger patients(OR=8.3) than in older patients. Foreign birth does confound, to some extent, the association of immunity with previous travel(OR =3.6) although the MH chi square and the 95% CI of OR_{MH} suggests that the association is still statistically significant. One notes some effect modification; thus, previous travel is of greater predictive value for immunity in U.S. born individuals than it is in foreign-born individuals.

Previous Pretravel Care and Hepatitis A Immunity

An attempt to find a correlation between a lack of previous pre-travel care and immunity failed to achieve statisitical significance. Since very few charts and very few recollections provided specific information on presence or absence of ISIG prophylaxis before some or all trips abroad, presumptive evidence had to be considered. For example, immunizations against yellow fever and cholera, or previous

use of antimalarials was considered as evidence of pre-travel medical care during which ISIG may have been administered. The absence of any such information, which was taken as evidence of no pre-travel medical care, may have been due instead, simply to omission of such data. Thus, the presumptive nature of the data may very well account for the inconclusiveness of this part of the study.

Destinations of Travel in Travel Clinic Patients

The destinations of immune and non-immune individuals were not subjected to statistical analysis because no trend was readily apparent in the destinations of the two groups. Furthermore, it would have been difficult to explain how any trend would reflect a greater probability of being immune. The destinations, however, represent a fair distribution in the areas shown to be of increased hepatitis A risk for travelers ie., Tropical Africa, South and Central America, Asia and North Africa. The data on attack rates do not enable one to make very refined estimates of risk for individual travelers. For example, attack rates are probably lower in the more developed areas of Southeast Asia such as Thailand, Hong Kong and Taiwan than they are in China, but the attack rate is only estimable for travel to Asia as a whole.

Purpose of Travel in Travel Clinic Patients

Likewise, purpose of travel probably influences one's risk for contracting hepatitis A , but data are not available for quantifying how it might do so. Intuitively, one would expect that business and study which took place in urban centers would pose the lowest risk while field research and volunteer work might pose the greatest risk. Traveling as a tourist probably presents a wide range of risks; whereas the Steffen study(28) did not show that the "roughness" of travel

affected incidence, the Danish study(32) demonstrated much higher attack rates in individual as opposed to group travelers. Five out of six immune individulals visiting relatives had been born in the developing country they were visiting, whereas none of the non-immune travelers visiting relatives were born outside of the U.S. This suggests that most travelers visiting relatives in a developing nation in which they themselves were born would probably already be immune. Presumably, visits to relatives could pose substantial risks to non-immune subjects since such visits might involve significant personal contact and living in households with very young, untoilet-trained children.

Assessment of Biases

Although nearly all patients entering the travel clinic were tested, the study was potentially subject to several types of biases. Informational bias is possible because conceivably, patients more likely to be immune may have experienced differential recall of past history, as they may have had a more sophisiticated knowledge of travel-related diseases since they were older, more likely to have been foreign-born and were more likely to have traveled previously. Observer bias was avoided either by questioning patients before test results were known, or by asking the same specific questions of both immune and non-immune individuals. Confounding bias results from the potential associations between the factors associated with immunity independent of their association with immunity. Mantel Haenzel (MH) analysis where possible and appropriate demonstrates some cases of confounding but in no cases did confounding remove all statistical significance from given odds ratios. Furthermore, the revelation of effect modification by subgroup analysis demonstrated

that some factors are (if odds ratios are interpreted as risk ratios) more predictive of immunity in the absence of other factors. This is in contrast to synergism, which might have occurred, if having multiple "risk factors" increased a given subject's chance of being immune.

The pervasive problem of selection bias is only somewhat problematic. Patients at travel clinics are clearly a self-selected population amongst travelers. Nevertheless, this study only concerns itself with patients who, for various reasons, refer themselves to travel clinics before travel to developing nations. The degree of selection bias introduced by the preponderance of older patients in the subjects tested by physician J.P. is not clear. Nevertheless, the effect of such a bias would be a potential underestimation of the association of increased age with immunity, an association already demonstrated in the age-prevalence portion of the study. The difference in follow-up of immune and non-immune patients was felt not to introduce a significant amount of selection bias since there were no apparent differences between non-immune individuals with complete charts and those without complete charts.

Summary

This study demonstrated a directly age-related increase in the prevalence of hepatitis A immunity in two university-affiliated travel clinic populations, with an overall prevalence of 15.5%. In the case-control aspect of the study, it was found that immune individuals were older, and were more likely to have been born outside of the U.S., to have a history of hepatitis and to have traveled to developing nations than were their non-immune controls. Conversely, gender, destination of travel, purpose of travel and evidence of previous pretravel medical care could not be shown to bear any relationship with HAV immunity.

Confounding and selection biases were found not to significantly affect the results of this study. On the other hand, MH analyses revealed several cases of effect-modification. Thus, increased age was shown to have a stronger association with HAV immunity in the absence of a concurrent history of previous developing nation travel. Likewise, foreign birth was associated more strongly with HAV immunity in younger patients than in older patients, and in patients without a history of hepatitis or of previous travel to developing nations. Finally, a history of hepatitis was found to have a stronger association with HAV immunity in U.S.-born individuals than in foreign-born individuals.

As has been discussed, travelers to developing nations are at risk for developing hepatitis A, which can be a serious disease. Classification of patterns of infection and avoidance of vehicles of transmission are not considered to be reliable means of control. The CDC, therefore,

recommends prophylaxis with ISIG. Although this procedure is safe, effective and relatively cheap, it must be repeated every four to six months for repeat or extended-stay travelers. Furthermore, conditions exist in which the safety, cost and convenience may be of concern to travelers, if not always to clinicians. Thus, serological screening for pre-existing hepatitis A immunity may be an alternative to routine ISIG prophylaxis, since immune individuals do not need ISIG.

This study has identified factors that may be associated with hepatitis A immunity in patients at U.S. travel clinics in general. The clinician can determine if a patient has any of these factors in a routine medical interview. Patients with one or some of these factors can be counselled on the possibility of serological determination of immune status instead of routine ISIG prophylaxis before travel to developing nations. Although this study does not provide the data necessary to design a cost-effective strategy for screening, it does, within the context of clinical judgment, allow the clinician to make an informed choice about whom to test. The patient who is found to be immune can thereby avoid unnecessary injections which are painful, and which may be associated with issues regarding safety, cost and convenience, which, though difficult to quantify, may be of considerable concern to the patient.

Furthermore, this study furnishes the groundwork for future research which could provide data necessary for the design of a cost-effective screening program. Populations with the factors identified in this study could be tested, to determine the prevalence of hepatitis A immunity in these groups, as compared with the prevalence in the general travel clinic population. Combined with potentially changing

concerns of cost and safety, these data would allow for the design of a cost-effective screening program.

In the interim, however, it is hoped that this study will enable some patients to avoid unnecessary injections of ISIG. Although the benefits derived thereby have been difficult to quantify, the opportunity to spare patients unnecessary pain, concern and inconvenience is a reasonable accomplishment of this clinical research project.

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